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EXAMINER

FORMAN, BETTY J

ART UNIT PAPER NUMBER

1634

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/425,633

Applicant(s)

CHEE ET AL.

Examiner

BJ Forman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-26, 29-31, 42-44, 46, 48 and 50-52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 25 July 2003 in which claims 26, 29-30, 42, 43-44, 46 and 49 were amended, claims 47 and 49 were canceled and claims 50-52 were added and further in view of the supplemental response filed 12 November 2003. All of the amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 4 April 2003, not reiterated below are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection necessitated by amendment are discussed.

Claims 23-26, 29-31, 42-44, 46, 48 and 50-52 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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3. Claims 23-26, 30, 31, 42-46, 48, 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al (U.S. Patent No. 5,952,174, issued 14 September 1999) in view of Weisburg et al (U.S. Patent No. 6,110,678, issued 29 August 2000).

Regarding Claim 42, Nikiforov et al teach a method of determining the identification of a nucleotide at a detection position in a target sequence comprising: providing a hybridization complex comprising a) a first target sequence comprising a first nucleotide at a detection position; a first target domain directly 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first ligation probe hybridized to said first target domain; and c) a second ligation probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that if the base of said dNTP is complementary to the base of said detection position, said first ligation probe is extended to form a ligation structure; contacting said ligation structure with a ligase to ligate said extended ligation probe and said second ligation probe to form a ligation product; and detecting the presence of said ligation product to identify the nucleotide at said detection position (Claim 1), said detection comprising providing a substrate with a surface comprising discrete sites and a capture probe i.e. a preferred 96-well microtiter plate (Column 10, line 63-Column 11, line 4 and Fig. 4) and they teach capture probes which hybridize to the ligation product (i.e. the first ligation probe is the capture probe) but they do not teach the discrete sites comprise microspheres comprising capture probes which hybridize to the ligation product. However, surfaces comprising microspheres comprising capture probes were well known in the art at the time the claimed invention was made as taught by Weisburg et al (Column 14, lines 58-67). Weisburg et al teach a similar method of determining a target comprising the steps of providing a hybridization complex comprising a) a first target sequence comprising a detection position; a first target domain 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first probe hybridized to said first target domain; and c) a second probe hybridized to said second target domain; contacting

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said hybridization complex with an extension enzyme and at least one dNTP such that said first probe is extended to form product; and detecting the presence of said product to identify the nucleotide at said detection position said detection comprising providing a substrate further comprising microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe which hybridizes to a sequence within said product (Column 11, lines 26-58 and Fig. 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions which permits optimization of both hybridization environment and capture environment (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes environmental conditions for numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

Regarding Claim 23, Nikiforov et al teach the method wherein a detectable label comprises a fluorophore (Column 13, lines 28-36).

Regarding Claim 24, Nikiforov et al teach the method wherein a detectable label comprises a biotin (Column 13, lines 28-36).

Regarding Claim 25, Nikiforov et al. teach the method of wherein said label is a hapten e.g. biotin (Column 13, lines 28-36) but they do not teach the hapten comprises imine-biotin. However, haptens comprising imine-biotin were known and routinely practiced in the art at the time the claimed invention was made and it was well known that imine-biotin and biotin are functionally equivalent labels. The courts have stated with regard to chemical homologs that

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the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the biotin label of Nikiforov et al. with functional equivalent and routinely practiced imine-biotin based on their equivalent functionality for the and based on available reagents and equipment and for the benefit of convenience and economy.

Regarding Claim 26, Nikiforov et al teach the method wherein the dNTP comprises a functional group for the addition of a fluorophore i.e. biotin hapten (Column 13, lines 28-36 and Fig. 4, step 5.).

Regarding Claim 30, Nikiforov et al teach the method wherein the substrate is selected from the group consisting of glass and plastic (Column 10, line 63-Column 11, line 4).

Regarding Claim 31, Nikiforov et al teach the method wherein a detectable label is a fluorophore (Column 13, lines 28-36).

Regarding Claim 43, Nikiforov et al teach the method wherein said ligation probe is captured by the solid support (Column 13, lines 21-24 and Fig. 4) but they do not specifically teach the ligation probe comprises an adapter sequence that hybridizes to said capture probe. However, Weisburg et al teach the similar method wherein said probe comprises an adapter sequence that hybridizes to said capture probe (Column 4, lines 23-35 and Fig 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions and therefore permits optimization of both hybridization and capture (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the

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extension product as taught by Weisburg et al to thereby optimize environmental conditions for the each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

Regarding Claim 44, Nikiforov et al teach the method wherein said dNTP comprises a detectable label (Column 7, line 65-Column 8, line 9 and Fig. 4).

Regarding Claim 45, Nikiforov et al teach the method wherein the first ligation probe is the capture probe (Column 3, lines 38-42).

Regarding Claim 46 (47), Nikiforov et al teach the method wherein the capture probe is a nucleic acid (Column 3, lines 38-42).

Regarding Claim 48 (49), Nikiforov et al teach the method wherein the discrete sites are wells (Column 10, lines 63-67).

Regarding Claim 50, Nikiforov et al teach a method of determining the identification of a nucleotide at a detection position in a target sequence comprising: providing a hybridization complex comprising a) a first target sequence comprising a first nucleotide at a detection position; a first target domain directly 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first ligation probe hybridized to said first target domain; and c) a second ligation probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that if the base of said dNTP is complementary to the base of said detection position, said first ligation probe is extended to form a ligation structure; contacting said ligation structure with a ligase to ligate said extended ligation probe and said second ligation probe to form a ligation product; and detecting the presence of said ligation product to identify the nucleotide at said detection position (Claim 1), said detection comprising providing a substrate with a surface comprising discrete sites and a capture probe i.e. a preferred 96-well microtiter plate (Column 10, line 63-Column 11, line 4 and Fig. 4) and they teach capture probes which hybridize to the

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ligation product (i.e. the first ligation probe is the capture probe) but they do not teach the discrete sites comprise microspheres comprising capture probes which hybridize to the ligation product. However, surfaces comprising microspheres comprising capture probes were well known in the art at the time the claimed invention was made as taught by Weisburg et al (Column 14, lines 58-67). Weisburg et al teach a similar method of determining a target comprising the steps of providing a hybridization complex comprising a) a first target sequence comprising a detection position; a first target domain 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first probe hybridized to said first target domain; and c) a second probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that said first probe is extended to form product; and detecting the presence of said product to identify the nucleotide at said detection position said detection comprising providing a substrate further comprising microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe which hybridizes to a sequence within said product (Column 11, lines 26-58 and Fig. 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions which permits optimization of both hybridization environment and capture environment (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes environmental conditions for numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

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Furthermore, Nikiforov et al teach the method wherein a second target sequence is detected i.e. oligonucleotides (Column 7, lines 16-19). Therefore, Nikiforov et al teach the method comprising formation of a second hybridization complex as claimed.

Regarding Claim 52, Nikiforov et al teach the method wherein said ligation probe is captured by the solid support (Column 13, lines 21-24 and Fig. 4) but they do not specifically teach the ligation probe comprises an adapter sequence that hybridizes to said capture probe. However, Weisburg et al teach the similar method wherein said probe comprises an adapter sequence that hybridizes to said capture probe (Column 4, lines 23-35 and Fig 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions and therefore permits optimization of both hybridization and capture (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for the each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

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4. Claims 29, 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al (U.S. Patent No. 5,952,174, issued 14 September 1999) in view of Weisburg et al (U.S. Patent No. 6,110,678, issued 29 August 2000) as applied to Claim 42 above and further in view of Walt et al (U.S. Patent No. 6,327,410, filed 11 September 1998).

Regarding Claim 29, Nikiforov et al teach a method of determining the identification of a nucleotide at a detection position in a target sequence comprising: providing a hybridization complex comprising a) a first target sequence comprising a first nucleotide at a detection position; a first target domain directly 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first ligation probe hybridized to said first target domain; and c) a second ligation probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that if the base of said dNTP is complementary to the base of said detection position, said first ligation probe is extended to form a ligation structure; contacting said ligation structure with a ligase to ligate said extended ligation probe and said second ligation probe to form a ligation product; and detecting the presence of said ligation product to identify the nucleotide at said detection position (Claim 1), said detection comprising providing a substrate with a surface comprising discrete sites and a capture probe (Fig. 4) i.e. a preferred 96-well microtiter plate (Column 10, line 63-Column 11, line 4) and they teach capture probes which hybridized to the ligation product (i.e. the first ligation probe is the capture probe)(Column 14, lines 58-67) and . Weisburg et al teach a similar method of determining a target comprising the steps of providing a hybridization complex comprising a) a first target sequence comprising a detection position; a first target domain directly 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first probe hybridized to said first target domain; and c) a second probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that said first probe is extended to form product; and detecting the presence of said product to identify the nucleotide at said detection

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position said detection comprising providing a substrate further comprising microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe which hybridizes to a sequence within said product (Column 11, lines 26-58 and Fig. 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions and therefore permits optimization of both hybridization and capture (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

Nikiforov et al and Weisburg et al do not teach the substrate is a fiber optic bundle. However, fiber optic bundle substrates were well known in the art at the time the claimed invention was made as taught by Walt et al. who teach a similar method of target detection comprising providing a hybridization complex and detecting the complex to identify the target wherein the detection comprises providing a substrate with a surface comprising discrete sites, further comprising a population of microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe and wherein the substrate is fiber optic bundle (Claim 17) wherein the fiber optic bundle substrate provides "extremely high density" substrate for detection of an extremely high number of targets (Column 5, lines 24-31). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fiber optic substrate of Walt et al to the substrate of Nikiforov et al and Weisburg et al for the obvious benefits of detecting an extremely

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high number of targets using the same substrate as taught by Walt et al (Column 5, lines 24-31).

Regarding Claim 49, Nikiforov et al teach the method wherein the target is randomly distributed i.e. 20 μ l aliquots of the PCR mixture are placed in each well (Column 17, lines 20-30) and Weisburg et al teach their microspheres are magnetically i.e. non-specifically attracted to the support (Column 14, lines 64-67) but Nikiforov et al and Weisburg et al do not specifically teach microspheres are randomly distributed on a substrate. However, Walt et al who teach the similar method also teach randomly distributed microspheres (Claim 17) wherein the random distribution is faster and less expensive than other distribution methods known in the art (Column 4, lines 53-56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the random distribution of Walt et al to the substrate distribution of Nikiforov et al and Weisburg et al for the obvious benefits of speed and economy as taught by Walt et al (Column 4, lines 53-56).

Regarding Claim 51, Nikiforov et al teach a method of determining the identification of a nucleotide at a detection position in a target sequence comprising: providing a hybridization complex comprising a) a first target sequence comprising a first nucleotide at a detection position; a first target domain directly 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first ligation probe hybridized to said first target domain; and c) a second ligation probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that if the base of said dNTP is complementary to the base of said detection position, said first ligation probe is extended to form a ligation structure; contacting said ligation structure with a ligase to ligate said extended ligation probe and said second ligation probe to form a ligation product; and detecting the presence of said ligation product to identify the nucleotide at said detection position (Claim 1), said detection comprising providing a substrate with a surface comprising discrete sites and a capture probe i.e. a preferred 96-well microtiter plate (Column

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10, line 63-Column 11, line 4 and Fig. 4) and they teach capture probes which hybridize to the ligation product (i.e. the first ligation probe is the capture probe) but they do not teach the discrete sites comprise microspheres comprising capture probes which hybridize to the ligation product. However, surfaces comprising microspheres comprising capture probes were well known in the art at the time the claimed invention was made as taught by Weisburg et al (Column 14, lines 58-67). Weisburg et al teach a similar method of determining a target comprising the steps of providing a hybridization complex comprising a) a first target sequence comprising a detection position; a first target domain 5' adjacent to said detection position; and a second target domain 3' adjacent to said detection position; b) a first probe hybridized to said first target domain; and c) a second probe hybridized to said second target domain; contacting said hybridization complex with an extension enzyme and at least one dNTP such that said first probe is extended to form product; and detecting the presence of said product to identify the nucleotide at said detection position said detection comprising providing a substrate further comprising microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe which hybridizes to a sequence within said product (Column 11, lines 26-58 and Fig. 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions which permits optimization of both hybridization environment and capture environment (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes environmental conditions for numerous methods e.g. primer extension and ligation (Column 7, lines 35-45). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by

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Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results.

Nikiforov et al and Weisburg et al are silent regarding random distribution of the immobilized capture probe. However, Walt et al teach random distribution of microspheres comprising capture probes and they teach motivation to use their random distribution i.e. "a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art." (Column 4, lines 53-56). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the random distribution of Walt et al to the immobilized capture probes of Nikiforov et al and Weisburg et al for the expected benefit of economy of time and expense as taught by Walt et al (Column 4, lines 53-56).

Response to Arguments

5. Applicant argues that Nikiforov does not teach the use of microspheres and does not teach first and second capture probes that hybridize to a first and second ligation product.

Applicant further argues that Weisburg et al does not teach first and second capture probes that hybridize to a first and second ligation product.

The arguments have been considered but are not found persuasive. Applicant appears to be arguing that the cited art does not teach first and second capture probes, targets and ligation produces wherein the first capture probes, targets and ligation produces are different from the second capture probes, targets and ligation produces. However, the claims are not so limited. Therefore, Applicant's arguments are not commensurate in scope with the claims.

Applicant argues that the examiner has not provided motivation to combine the teaching of Nikiforov and Weisburg. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Nikiforov and Weisburg both teach methods similar to that claimed. Nikiforov teach the method wherein the said detection comprising

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providing a substrate with a surface comprising discrete sites and a capture probe i.e. a preferred 96-well microtiter plate and they teach capture probes which hybridize to the ligation product (i.e. the first ligation probe is the capture probe) (Nikiforov: Claim 1, Column 10, line 63-Column 11, line 4 and Fig. 4) and Weisburg teach the method providing a substrate further comprising microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe which hybridizes to a sequence within said product (Column 11, lines 26-58 and Fig. 3) wherein their capture probe hybridization permits target-probe hybridization and target-capture probe hybridization to occur under different environmental conditions which permits optimization of both hybridization environment and capture environment (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes environmental conditions for numerous methods e.g. primer extension and ligation (Column 7, lines 35-45).

As stated above, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture of Nikiforov et al by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions for each method step (i.e. hybridization, primer extension, ligation and capture) as suggested by Weisburg et al (Column 4, lines 57-Column 5, line 19) for the obvious benefits of maximizing experimental results i.e. facilitating hybridization (Weisburg et al, Column 5, lines 1-19).

Applicant "is puzzled" by the "maximizing experimental results cited by the office because the statement is based on some generic reasoning involving "mysterious" maximization and therefore legally incorrect. The argument has been considered but is not found persuasive because as stated above, Weisburg et al specifically teach (as cited above) their two-step hybridization maximizes experimentally i.e. permits optimization of both hybridization environment and capture environment (Column 4, line 57-Column 5, line 19) and wherein the capture probe hybridization of Weisburg et al optimizes environmental conditions for numerous methods e.g. primer extension and ligation (Column 7, lines 35-45).

It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Applicant argues that the combination of Nikiforov and Weisburg would require a minimum of five oligonucleotides and therefore adding two additional oligonucleotides to the method of Weisburg which one of ordinary skill would recognize as additional steps, time and potentially minimizing results. The argument has been considered but is not found persuasive. Applicant's interpretation of the combination of Nikiforov and Weisburg is interesting, however,

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the interpretation is not relevant to the instant claims or rejection. Furthermore, the instant claims do not limit the capture probe such that it's different from either the first or second ligation probe.

Applicant argues that the hybridization requirements of Nikiforov teach away from and the combination of Nikiforov and Weisburg and render the combination inoperable. The argument has been considered but is not found persuasive because the argument does not address limitations of the claims. Therefore, the argument is not relevant to the instant rejection.

Applicant argues that there is no motivation to combine the teaching of Walt et al with that of Nikiforov and Weisburg because Walt et al does not overcome the problems of combining Nikiforov and Weisburg i.e. requirement of additional oligonucleotides and different hybridization temperatures. The argument has been considered but is not found persuasive for the reasons stated above regarding Nikiforov and Weisburg.

Response to Applicant's Remarks and Declaration by Dr. Stueplnagel

6. Applicant argues that a clear nexus between the claimed invention and the commercial success of Illumina's platform has been established. Applicant cites a Illumina's participation in HapMap which "comprises the use of an optical fiber array in which each fiber is capped with a silica bead coated with DNA probes, wherein different DNA sequences in the test samples bind to the probes on each particular bead." Applicant cites additional illustration of the HapMap using Illumina's platform. The arguments have been considered but are not found persuasive because the instant claims are drawn to a method, not a product i.e. Illumina's platform. Furthermore, the instantly claimed methods are drawn to a method for determining the identification of a nucleotide at a detection position. The claims are not limited to an optical fiber array. The claims are not limited to each fiber being capped with a silica bead. The claims are not limited to silica beads. The claims are not limited to different DNA sequences from a sample binding to probes on a particular bead. Therefore, Applicant's

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comments regarding the commercial success of Illumina's platform and use of the platform in the HapMap project are not commensurate in scope with the instant claims.

Applicant's arguments and illustrations of commercial success are not deemed as sufficient evidence of nonobviousness because Applicant has not clearly established a nexus between the claimed invention and commercial success.

An applicant who is asserting commercial success to support its contention of nonobviousness bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success (see MPEP, 716.03).

The courts have stated that when considering evidence of commercial success, **care should be taken to determine that the commercial success alleged is directly derived from the invention claimed**, in a marketplace where the consumer is free to choose on the basis of objective principles, and that such success is not the result of heavy promotion or advertising, shift in advertising, consumption by purchasers normally tied to applicant or assignee, or other business events extraneous to the merits of the claimed invention, etc. *In re Mageli*, 470 F.2d 1380, 176 USPQ 305 (CCPA 1973) and *In re Noznick*, 478 F.2d 1260, 178 USPQ 43 (CCPA 1973).

In ex parte proceedings before the Patent and Trademark Office, an applicant must show that the claimed features were responsible for the commercial success of an article if the evidence of nonobviousness is to be accorded substantial weight. See *In re Huang*, 100 F.3d 135, 140, 40 USPQ2d 1685, 1690 (Fed. Cir. 1996) (Inventor's opinion as to the purchaser's reason for buying the product is insufficient to demonstrate a nexus between the sales and the claimed invention.). Merely showing that there was commercial success of an article which embodied the invention is not sufficient. *Ex parte Remark*, 15 USPQ2d 1498, 1502-02 (Bd. Pat. App. & Inter. 1990).

An affidavit or declaration attributing commercial success to a product or process "constructed according to the disclosure

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and claims of [the] patent application" or other equivalent language **does not establish a nexus between the claimed invention and the commercial success** because there is no evidence that the product or process which has been sold corresponds to the claimed invention, or that whatever commercial success may have occurred is attributable to the product or process defined by the claims. Ex parte Standish, 10 USPQ2d 1454, 1458 (Bd. Pat. App. & Inter. 1988).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 29-31, 42-43 and 46-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 27-30 of U.S. Patent No. 6,355,431. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to similar methods comprising the steps of providing a hybridization complex, contacting the complex with an extension enzyme, and a ligase to form a ligation product and detecting by contacting the product with a population of microspheres at discrete sites on a surface. The claim sets differ

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only in the arrangement of the limitations. For example, instant Claim 42 (from which all other pending claims depend) recites contacting with a ligase to form a ligation product while dependent claim 7 of the '431 patent recites this further limitation. While the claim sets differ in the arrangement of limitations, instant claims 29-31, 42-43 and 46-48 and 1-7 and 27-30 of the '431 not patentably distinct because the claim sets encompass similar methods comprising the same method steps reciting the same limitations.

Response to Arguments

9. Applicant argues that the instantly claimed methods for determining the identification of a nucleotide at a detection position are patentably distinct from the '431 methods for detecting a nucleotide sequence rather than a nucleotide. The argument has been considered but is not found persuasive because the instant claims are drawn to a method "comprising" detecting the ligation product to identify the nucleotide. The open claim language "comprising" encompasses detection of the nucleotide sequence and furthermore, the instantly claimed the identification of a nucleotide, by definition detects the nucleotide sequence. Therefore, the instant claims are obvious in view of the '431 method. The rejection is maintained.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741 until 13 January 2004. The examiner can normally be reached on 6:00 TO 3:30 Monday through Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0507.



BJ Forman, Ph.D.
Primary Examiner
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January 28, 2004